

A review of multisite pacing to achieve cardiac resynchronization therapy

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Received 26 February 2014; accepted after revision 12 June 2014; online publish-ahead-of-print 11 September 2014

Non-response to cardiac resynchronization therapy remains a significant problem in up to 30% of patients. Multisite stimulation has emerged as a way of potentially overcoming non-response. This may be achieved by the use of multiple leads placed within the coronary sinus and its tributaries (dual-vein pacing) or more recently by the use of multipolar (quadripolar) left ventricular pacing leads which can deliver pacing stimuli at multiple sites within the same vein. This review covers the role of multisite pacing including the interaction with the underlying pathophysiology, the current and planned studies, and the potential pitfalls of this technology.

Keywords

Cardiac resynchronization therapy • Dyssynchrony • Heart failure • Pacemaker • Multisite pacing

Introduction

The problem of cardiac resynchronization therapy non-response

Cardiac resynchronization therapy (CRT) is one of the most successful heart failure therapies to emerge in the last 25 years and is applicable to 25–30% of patients with symptomatic heart failure.¹ Large randomized trials have demonstrated that CRT improves quality of life (QoL), reduces heart failure hospitalizations and mortality, and reverses the structural remodelling of the heart.² Clinical response to CRT is, however, variable with up to one-third of patients not responding.^{3,4} Patient selection, inadequate delivery of cardiac resynchronization, and suboptimal left ventricular (LV) lead position are all important causes of non-response.⁵ The pre-requisite for response to CRT is electrical dyssynchrony manifest on the surface electrocardiogram (ECG) usually as left bundle branch block (LBBB). In keeping with this patients with narrower QRS width and non-LBBB morphology fare worse in terms of CRT response.^{6,7} In an effort to improve CRT response, alternative methods of CRT delivery, including multisite pacing (MSP), have been developed. Pacing the LV from more than one coronary sinus (CS) site simultaneously can improve

acute haemodynamic response (AHR) and medium-term outcomes. The implantation of two separate CS leads is technically challenging and recently introduced multipolar LV leads have the ability to deliver MSP through a single CS LV lead.

Physiological scientific rationale for multisite pacing

Even among patients with LBBB, there is heterogeneity in the location of conduction block and resulting LV activation pattern.^{8,9} Two broad patterns of LV activation have been described with electroanatomical mapping: type I activation, with slow propagation from the septum to lateral wall, and type II activation with a U-shaped activation pattern resulting from a line of functional conduction block. A type II activation pattern would be expected to be more amenable to correction by LV stimulation, and indeed this pattern is associated with a favourable response to CRT.⁹ A further determinant of CRT response may be the presence, location, and burden of myocardial scar and the position of the LV lead with respect to these regions.^{10–14} Implantation of an LV lead in an area of myocardial scar may be associated with slow conduction and block resulting in less haemodynamic improvement and a poor clinical outcome.¹⁵ Cardiac resynchronization therapy

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What's new?

- Non-response to CRT occurs 30% of patients.
- Multisite LV (MSLV) stimulation may overcome non-response.
- MSLV achieved with multiple leads placed within the coronary sinus (dual-vein pacing) or using multipolar (quadripolar) LV pacing leads.
- Review of underlying pathophysiology, the current and planned studies, and the potential pitfalls of MSLV.

exerts its beneficial effects by more than one mechanism, but perhaps the most important contributing factor is restoration of intra-LV synchrony.^{16,17} Central to this is the rapid and uniform electrical activation of the LV. This can be accomplished in a subgroup of patients by appropriate atrioventricular (AV) timing achieving activation of the LV from multiple widely separate sites [via intrinsic conduction, trans-septal conduction from the right ventricular (RV) pacing site, and activation from the LV pacing site]. There is some suggestion that to synchronize effectively, the RV and LV leads should be positioned as far from each other as possible.¹⁸ Current strategies involve the placement of leads 'anatomically' rather than using more patient-specific physiological approaches and the site of LV lead placement remains controversial with the final position of the LV pacing lead dictated by the cardiac venous system anatomy, the performance and stability of the pacing lead, and the absence of phrenic nerve stimulation (PNS). The COMPANION¹⁹ and MADIT-CRT²⁰ studies showed a comparable response between lateral, anterior, or posterior LV lead locations, while data from the REVERSE-HF²¹ maintain the potential benefit of a lateral lead location. The TARGET and the STARTER studies showed that guided placement of the LV lead over the segment of maximal mechanical dyssynchrony and avoidance of scar can improve the magnitude of reverse remodelling and clinical outcomes.^{22,23}

Historically, significant attention has been placed on the technical aspects of the implant procedure, particularly the placement of the transvenous epicardial LV lead has been critical to achieving cardiac resynchronization. It is known that the optimal site of AHR to CRT varies between patients and therefore may need to be individualized.^{24–26} In an effort to improve CRT response, alternative methods of CRT delivery, including LV endocardial and epicardial MSP have been developed. Pacing the LV endocardially or from more than one CS site has been shown to improve CRT response.^{26–33} Recently introduced multipolar LV leads have the potential to deliver stimulation through multiple electrodes from a single lead.^{34,35} As the benefits of CRT are predominantly thought to result from improved LV electrical resynchronization, the concept of MSP has arisen as an alternative strategy for improving CRT success rate. Human data with MSP are restricted to a small number of pacing sites due to the CS anatomy; however, animal studies are not limited by this constraint. In the canine model, Ploux et al.³⁶ recently assessed the effect of MSP on haemodynamics and electrical activation in nine anaesthetized dogs with chronic LBBB where up to seven LV epicardial electrodes were placed. Each electrode was tested alone and in combination with the other electrodes. Single-site LV pacing provided a significant increase in acute haemodynamic measures ($LVdP/dt_{max}$) and was incrementally increased by

the addition of further pacing electrodes. Notably however, the improvement in $LVdP/dt_{max}$ was limited to conditions where single-LV pacing provided suboptimal improvement. There is considerable heterogeneity in the myocardial substrate of patients receiving CRT, in particular in the aetiology of heart failure and the location of conduction block within the heart that may account for variability in CRT response.^{8,9} A non-contact mapping study of the underlying myocardial substrate in patients receiving CRT³⁷ showed that the majority of patients with a non-ischaemic heart failure aetiology or functional block responded to conventional single-site CRT, whereas those with myocardial scar or the absence of functional block often required MSP to achieve CRT response. It is possible therefore that MSP may be required in certain subsets of patients undergoing CRT, particularly those patients with ischaemic cardiomyopathy and with narrower QRS who may benefit from novel pacing strategies.

Delivery of multisite pacing

Multiple leads

The concept of MSP using multiple leads is based on the hypothesis that pacing at multiple points within the ventricles will improve cardiac resynchronization. Two different pacing modalities have been proposed using multiple leads: the first using two RV leads and one LV lead, the second using one RV lead and two LV leads inserted in the two separate tributaries of the CS. (Figure 1) Yoshida et al.³⁸ studied the acute haemodynamic benefit of triple-site pacing with two RV leads and one LV lead compared with conventional biventricular pacing in 21 patients. One RV lead was positioned

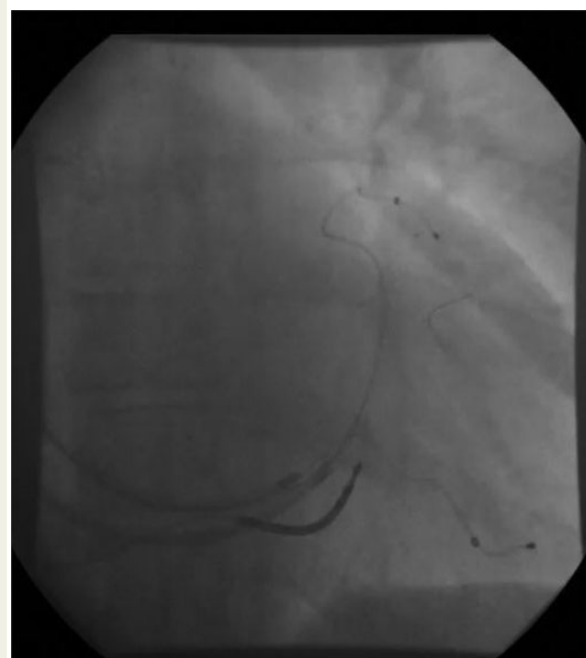


Figure 1 Anteroposterior projection of deployment of two bipolar LV pacing leads in separate branches of the CS (anterolateral and posterolateral) to achieve dual LV lead CRT.

at the RV apex and the second in the RV outflow tract. $LVdP/dt_{max}$ and cardiac output were significantly improved with triple-site pacing compared with biventricular pacing. The authors also found an acute reduction in LV end-systolic volume (LVESV) and an acute increase in LVEF, although the differences were small. Finally, they showed that bifocal RV and LV pacing were superior to biventricular pacing in acutely improving mechanical dyssynchrony. The advantage of this concept is that implantation of two RV leads may be technically easier than two LV leads; however, this pacing configuration has yet to be evaluated chronically in a prospective randomized trial. The use of two LV leads was initially tested with acute haemodynamic studies with conflicting results. Pappone *et al.*³⁹ demonstrated a significant improvement in $LVdP/dt_{max}$, pulse pressure, and LV end-diastolic pressure with dual-site LV pacing. Padeletti, however, did not show a significant haemodynamic improvement with dual-vein LV pacing at the optimal AV delay if the first lead was positioned optimally.³¹ Ginks *et al.* found that dual-vein LV pacing increased $LVdP/dt_{max}$, but that this effect was only marked in patients with posterolateral scar.³³ The feasibility of chronic implantation of two leads into the CS has been shown with a success rate of 85–95% and encouraging mid-term follow-up results.^{29,30} In a randomized crossover trial (TRIP-HF) including 42 patients with permanent atrial fibrillation and a CRT indication, Leclercq *et al.*²⁹ showed that dual-vein LV pacing did not improve New York Heart Association (NYHA) class, 6 min walk test (6 MWT), and QoL compared with conventional biventricular pacing but did yield a significant improvement in LVEF and LVESV at 3 months follow-up. Lenarczyk *et al.*³⁰ in a non-randomized study compared 27 patients with biventricular pacing and 27 with dual-vein LV pacing and showed that the magnitude of improvement in symptoms and LVEF was higher with dual-vein LV pacing. The Trust CRT trial, a randomized trial including 98 patients, showed that dual-site LV pacing significantly increased CRT response based on the NYHA class as compared with biventricular pacing.⁴⁰ Rogers *et al.* in a double-blind randomized crossover trial compared MSP with conventional biventricular pacing in 43 patients.³² Two groups were identified: Group A with two CS leads and one RV lead and Group B with two RV leads (septum and apex) and one LV lead. The primary endpoint was the comparison at 3 months of 6 MWTs which was significantly increased with MSP compared with standard CRT (451 ± 112 vs. 425 ± 119 m, $P = 0.008$). Interestingly, a significant improvement in LVEF and LVESVs were also observed but only in Group A. Recently, Ogano *et al.*⁴¹ reported a potential antiarrhythmic effect of dual-vein LV pacing in 58 patients. During a mean follow-up of 481 days, ventricular arrhythmias occurred in 2 of 22 patients in the dual-site LV pacing and 14 of 36 in the standard CRT group with ventricular indices of QT, JT intervals and transmural dispersion of repolarization significantly shortened at 6 months with dual-site LV pacing compared with standard CRT.

Multisite pacing with multiple pacing leads (dual-vein LV pacing) could be a potential solution for patients who do not respond to conventional CRT. The V3 trial⁴² has recruited 100 non-responder patients randomized to triple-site pacing with addition of a second LV lead into the CS or to a control group, with the primary endpoint being the clinical composite score at 12 months and the results are awaited. At present, MSP using multiple pacing leads is feasible with a high implantation success rate and preliminary small studies have shown encouraging results. However, the power of these studies is

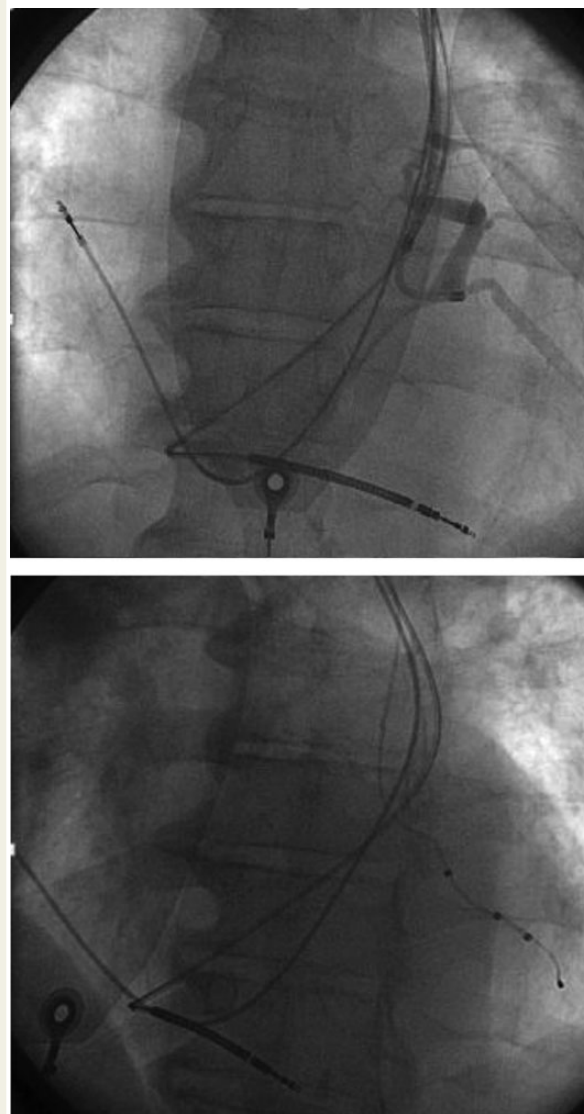


Figure 2 Top: Anteroposterior projection. Coronary sinus angiography performed with a telescopic catheter placed into a lateral cardiac vein. Bottom: LAO 30° projection. Implantation of a quadripolar LV lead using a similar approach compared with a regular bipolar LV lead. The patient has a persistent left-sided superior vena cava.

limited and we do not at present have enough evidence to consider this pacing modality as a first-line therapy. Further prospective clinical investigations are needed with a clear evaluation of the clinical benefit and also the adverse events.

Multipolar leads and cardiac resynchronization therapy

The alternative approach to deliver MSP rather than via multiple leads is using a multipolar lead capable of delivering the multiple LV stimulation sites (Figure 2). Quadripolar leads to pace the LV can now deliver resynchronization therapy with the first report of human

use in 2010.⁴³ Since then, there have been numerous reports on the safety and efficacy of quadripolar leads both in single-centre^{44–45} and multicentre settings.^{47–49} Implant success rates have been above 95% and mid-term data confirm that quadripolar leads offer good stability with satisfactory dislodgement rates ($\leq 3\%$) and stable performance in terms of pacing threshold.^{44–49} High capture thresholds and PNS still represent an important limitation to deliver CRT with bipolar leads in up to 30% of patients and unfortunately these problems may arise at follow-up in a significant proportion of the patients. The expression ‘electronic repositioning’ has been used to describe the possibility to overcome these issues by device reprogramming, either by selecting different pacing vectors and/or by adjusting pacing output to assure LV capture and avoiding PNS. Despite this, a small percentage of patients (1–2%) who may need a reintervention or worse will be deprived of resynchronization therapy.^{50–52} Quadripolar leads offer evident advantages by offering more pacing configurations (up to 17 vs. up to 6), which may alleviate the problem of high thresholds, avoid PNS, or at least offer an adequate safety margin (LV vs. phrenic nerve capture).^{53–55} Anatomy of the coronary venous system and phrenic nerve course can sometimes be challenging and there have been cases where only one of the multiple pacing configurations could be used⁵⁶ and one failure where no good configurations were found.⁵⁷ Of note, the use of conventional bipolar leads would not have solved these issues. Ohlow et al.⁵⁸ reported implant success with a quadripolar lead in 24 of 26 patients for whom at least two different attempts with conventional biventricular leads had failed. The use of different quadripolar single-site pacing vectors/configurations on acute CRT response has been evaluated in small studies. Shetty et al.⁵⁹ studied the AHR to LV pacing within individual branches of the CS using a quadripolar lead and found greater differences when pacing in different CS branches compared with pacing along the same branch of the CS. Asbach et al.⁶⁰ studied different vector selections of a quadripolar LV pacing lead and showed that an individually optimized configuration gave rise to an additional absolute 10% increase $LVdP/dt_{max}$ when comparing optimal and worst vectors. Several studies have also shown changes in LV electrical activation with a quadripolar lead.^{61,62}

The next logical question is whether MSP using multipolar pacing configurations can improve CRT response. To address this important question, we only have preliminary data from small acute studies

(Table 1) and this type of pacing should still be considered experimental, with only preliminary results. Several small studies suggest that maximization of CRT can be obtained through individualization of MSP configuration with improvements in haemodynamic response and dyssynchrony.^{63–65} Thibault et al.⁶³ in an acute haemodynamic study showed that in 72% of the patients, MSP from a quadripolar lead improved acute systolic function compared with conventional biventricular pacing, with stimulation from the most distal and proximal electrodes most commonly yielding the greatest $LVdP/dt_{max}$. Pappone et al.⁶⁴ studied 44 patients using pressure–volume loops and showed that MSP could significantly improve acute response compared with conventional CRT. Rinaldi et al.^{65,66} in a multicentre study showed acute improvements in dyssynchrony with MSP and more recently improvements in radial strain. A recent study by Shetty et al.⁶⁷ compared MSP using multiple CS leads (dual LV lead), with MSP delivered via a single quadripolar lead. Notably, there was a similar increase in $LVdP/dt_{max}$ with dual-vein LV pacing and single-vein MSP compared with conventional CRT, but this was not statistically significant. Within individuals, however, different methods of stimulation are optimal and may need to be tailored to the underlying substrate. Studies using biophysical modelling have suggested that MSP from a quadripolar lead may exert its benefit mainly in patients with an ischaemic aetiology and LV scar.⁶⁸

Potential complications and pitfalls of multisite pacing

Although attractive from a pathophysiological view,⁶⁹ dual-vein MSP to achieve CRT is hindered by several clinical and technical issues. Ogano et al.⁴¹ showed only 55% of patients had acute improvements with dual-vein LV pacing compared with conventional CRT with no difference in reverse remodelling at follow-up. This observation emphasizes the need to identify the optimal LV lead placements for MSP, which is currently unclear. In most studies, the great cardiac vein⁴¹ or inferior/anterolateral veins^{7,28,32} were used for the second LV lead in addition to the standard posterior-lateral vein placement. The optimal placement of the LV lead varies between individuals^{25,27} and dual-vein LV lead pacing may be viewed as an attempt to overcome the target site selection process by addressing multiple accessible sites.

Table 1 Studies of MPS delivered by a quadripolar

Author, year	Number of patients	Study type	Findings
Thibault et al. (2013)	19 (21)	Acute comparative study Measurement: invasive haemodynamic evaluation (dP/dt)	72% of patients, MPP improved acute systolic function vs. conventional CRT. Pacing most distal and proximal electrodes most commonly yielded greatest $LVdP/dt_{max}$
Rinaldi et al. (2013)	41(52)	Comparative study after implant Measurement: echocardiographic dyssynchrony (TDI)	64% of patients MPP resulted in significant reduction in dyssynchrony vs. conventional CRT
Pappone et al. (2013)	44	Randomized comparative study at the time of implant Measurement: invasive haemodynamic evaluation (pressure–volume loops)	Main finding: CRT with MPP can significantly improve acute LV haemodynamic parameters assessed with PV loop measurements as compared with conventional CRT

Technical issues

Issues with multivein pacing

Dual-vein LV pacing may be expected to have a complication rate higher than conventional CRT. The overall implant duration and fluoroscopic exposure may be longer than for standard CRT system implantation,⁴⁰ potentially exposing the operator to the harmful effects of ionizing radiation and the patient to an increased risk of device infection. Reported complication rates with dual-vein LV pacing cannot be generalized, owing to the fact that centres undertaking these procedures are usually high-volume centres reporting high success rates^{28,29,32,40} that may not directly translate to smaller volume centres. In one study, the success rate to place a second LV was 100%;⁴¹ however, in the study by Rogers *et al.*,³² 46% of patients could not be successfully implanted with a second LV lead. Data on short- and mid-term complications associated with dual-vein LV pacing systems are limited with a complication rate that may be higher than conventional CRT.^{29,30} In the TRIP-HF study after a 9-month follow-up of 40 patients, the rate of complication was not negligible with 5 patients suffering from PNS, 4 patients demonstrating lead dislodgement, and 2 patients having their CRT system explanted because of infection.²⁹ In a more recent study in patients implanted with current tools and devices, the incidence of serious complications at 1 year was comparable in patients with dual-vein LV pacing compared with conventional CRT with no increase in the rates of PNS or lead dislodgement.³⁰ Indeed, it is possible that the presence of two leads inside the CS may increase their stability from a physical point of view compared with a single lead,⁷⁰ but this needs to be proven in larger patient populations. The median follow-up in the four reported studies of chronic dual-vein LV pacing is 6 months,^{29,30,32,41} which is inadequate to assess safety in the long term. Overall, 3 of 97 patients (3%) in these studies^{29,30,32,41} underwent device removal because of pocket infection and 1 patient died of sepsis unrelated to the device. In a pooled analysis of the three largest studies,^{29,30,32} the occurrence of PNS that could not be managed electronically contributed to the inability to place a second LV lead in 9 of 103 patients (8.9%). The situation may be particularly difficult to manage in the presence of a low phrenic threshold (3–4 V) at one site coupled with a high (2–3 V) LV threshold at the other site. The risk of LV lead dislodgement or loss of LV capture is increased when lead repositioning to a more proximal site is required to prevent PNS,⁷¹ a problem which may be better overcome with multipolar leads which allow distal positioning of the lead and stimulation from a proximal electrode. The avoidance of PNS could potentially be achieved by dedicated devices with two LV ports coupled to multipolar LV leads, that could address PNS at no compromise with the targeted coronary vein or LV stimulation site;^{72,73} however, the development of dedicated devices with more than one ventricular port would not appear to be in the current plans of the device companies.

Currently available CRT devices have only two ventricular ports and to deliver dual-vein LV pacing, the two LV leads are generally connected to the single ventricular port using a parallel bipolar Y-connector. This type of connection results in a significant drop in LV pacing impedance in ~20% of patients³⁰ and a large increase in current delivery. Compared with conventional resynchronization, the resulting high current drain will dramatically reduce the device longevity. Moreover, Y-connectors are bulky and may predispose

to skin erosion. Effective dual-vein LV pacing may also be difficult to confirm when performing LV pacing thresholds: a 12-lead ECG is required to analyse the sometimes discrete QRS morphology changes between dual- and single-vein LV lead capture.

Potential for pro-arrhythmia

The issue of the effect of CRT on arrhythmia burden is controversial, with LV and biventricular pacing suspected to be pro-arrhythmic with an increase in transmural heterogeneity of repolarization in some patients,⁷⁴ whereas CRT seems to have a protective effect against ventricular arrhythmias in others.⁷⁵ The effect of the increased number of LV pacing sites is unclear. In dogs with chronic LBBB,³⁶ multisite LV pacing with seven epicardial electrodes did not induce ventricular arrhythmias acutely, and increasing the number of LV sites was associated with a reduction in the duration of the corrected QT interval. Acute studies of multisite LV pacing with a quadripolar lead have not shown any acute ventricular arrhythmia;⁶⁵ however, long-term studies are required to demonstrate safety.

Currently, there is no evidence that dual-vein LV pacing with separate CS leads can improve further the overall success rate of CRT. The current technology does not allow the easy use of this technique: the implantation is far more complex than the standard procedure and the connection difficulties are problematic. Lack of data on long-term complications such as loss of LV capture, premature generator exhaustion (predisposing to device infection) due to the high current drain, and skin issues related to increased pocket hardware prevent us from reporting a full picture of dual-vein LV lead complications against conventional CRT. At present, dual-vein LV pacing may be proposed in patients with poor prognosis and limited life expectancy or those who have not responded to standard CRT; the potential clinical benefit, if demonstrated, may outweigh the device longevity reduction. The use of multipolar electrodes to allow MSP may be associated with less complications and downsides; however, we only have very preliminary data.

Ongoing, planned studies and future directions

Conventional CRT using quadripolar LV pacing leads and single-site LV stimulation have been shown to be safe and reliable in the short- and mid-term.^{44–49} As with any new technology, longer-term data are needed from ongoing studies evaluating the acute and chronic performance of quadripolar leads.^{76–79} The multiple vectors offered by multipolar leads provide more options to select the best LV pacing configuration that allow good capture threshold and avoid PNS and this new technology may offer benefits in terms of CRT response. Conduction disturbance and electrical dyssynchrony remain complex phenomena, and pacing the LV from multiple points may prove helpful to overcome some of the issues due to scar and areas of disturbed conduction. Multiple pacing electrodes on the same LV lead also offer the ability to pace simultaneously and sequentially from multiple LV sites. There are currently two randomized controlled studies evaluating the efficacy of multisite LV pacing with quadripolar leads on patient outcomes. The MultiPoint Pacing IDE Study (NCT01786993) is a prospective, randomized, double-blind, multicentre study conducted in the USA that will enrol up to 506 patients with a standard CRT indication.⁸⁰ Patients will be

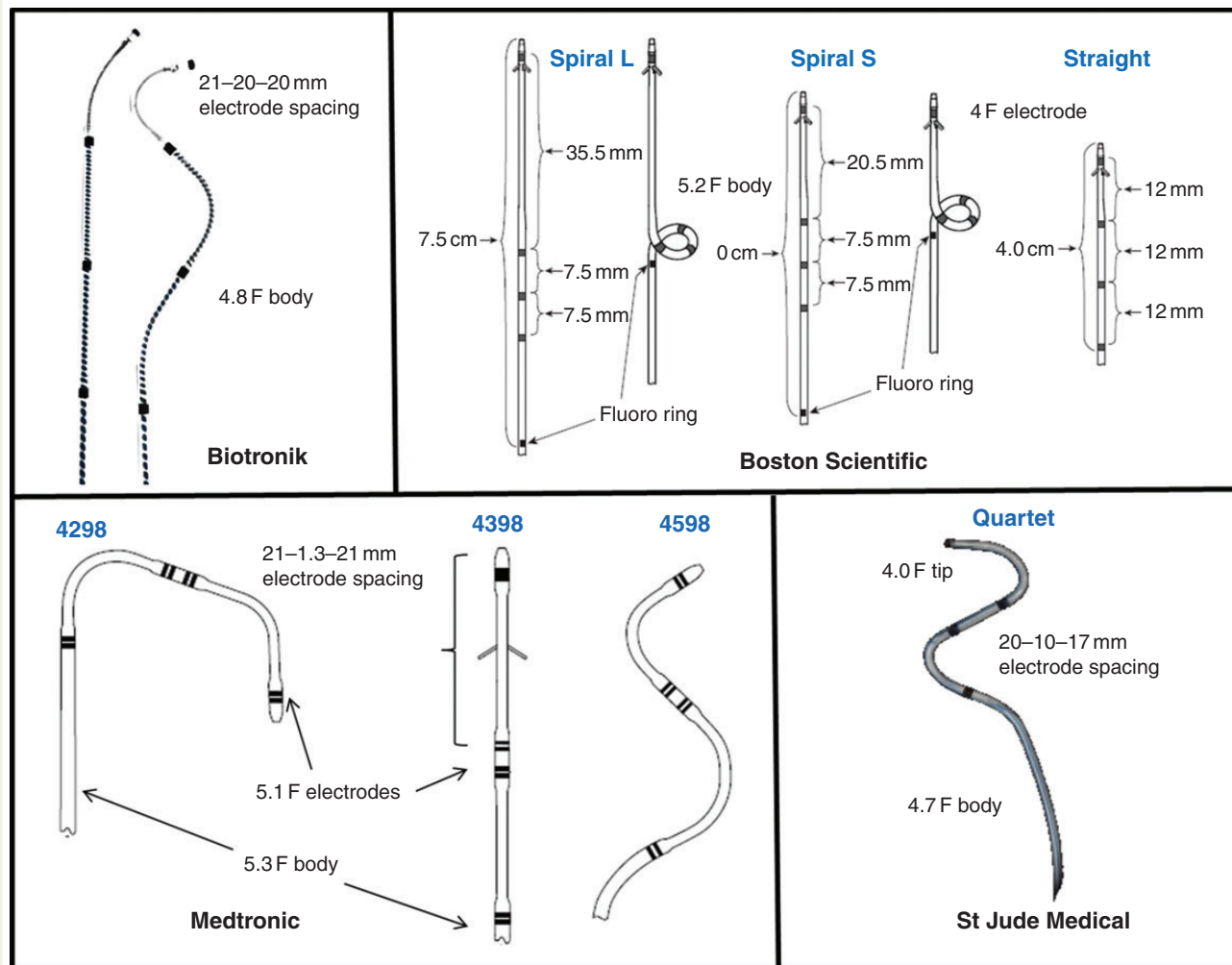


Figure 3 Currently available quadripolar LV leads, showing differences in lead design (reproduced/adapted and with permission from Boston Scientific, St Jude Medical, and Medtronic).

randomized to implantation with either a quadripolar or a standard bipolar CRT-defibrillator (CRT-D) system. The two primary end-points are freedom from system-related complications and percentage of non-responders (defined by a clinical composite score) at 9-months follow-up. The study was initiated in April 2013, and is expected to terminate in 2015. The MORE REsponse on Cardiac Resynchronization Therapy With MultiPoint Pacing (MORE-CRT MPP) (NCT02006069) is a prospective, randomized, double-blind, multicentre study that will be conducted in Europe, Canada, and other non-US centres, enrolling ~1250 patients with a standard CRT indication.⁸¹ All patients will be implanted with a CRT system with a quadripolar lead and initially programmed to standard biven-tricular pacing with bipolar pacing from a single vector of the lead. At 6 months, non-responders (defined as patients with a <15% reduction in LVESV of compared with baseline) will be randomized to ongoing standard bipolar stimulation or multipoint pacing with stimulation via multiple vectors from the quadripolar lead. The primary endpoint is the percentage of non-responders converted

to responders (>15% reduction in ESV) after a further 6 months follow-up. The first patient was enrolled in December 2013, and the study is expected to terminate in 2017.

For dual-vein LV pacing, a Y-adapter with two IS-1 inputs and an IS-4 output would be very useful to facilitate LV threshold measurements and programming. Several device companies currently offer quadri-polar LV leads (Figure 3). The variety of lead designs within or across the different manufacturers offers solutions that may suit individual patient venous anatomies. The connectors are all IS-4, which means that they can be used interchangeably. However, currently only one company has CRT-D generators currently offering MSP from a quadripolar lead, although other manufacturers may also do so in the future. No CRT-pacemaker device is currently capable of delivering MSP, but this also is expected to be available in the future.

An important step will be to define how to optimize programming of MSP, as little is known so far regarding this issue. It has been shown that the configuration that most frequently yielded the best acute dP/dt_{\max} measurement was the tip + proximal electrodes (in 42%

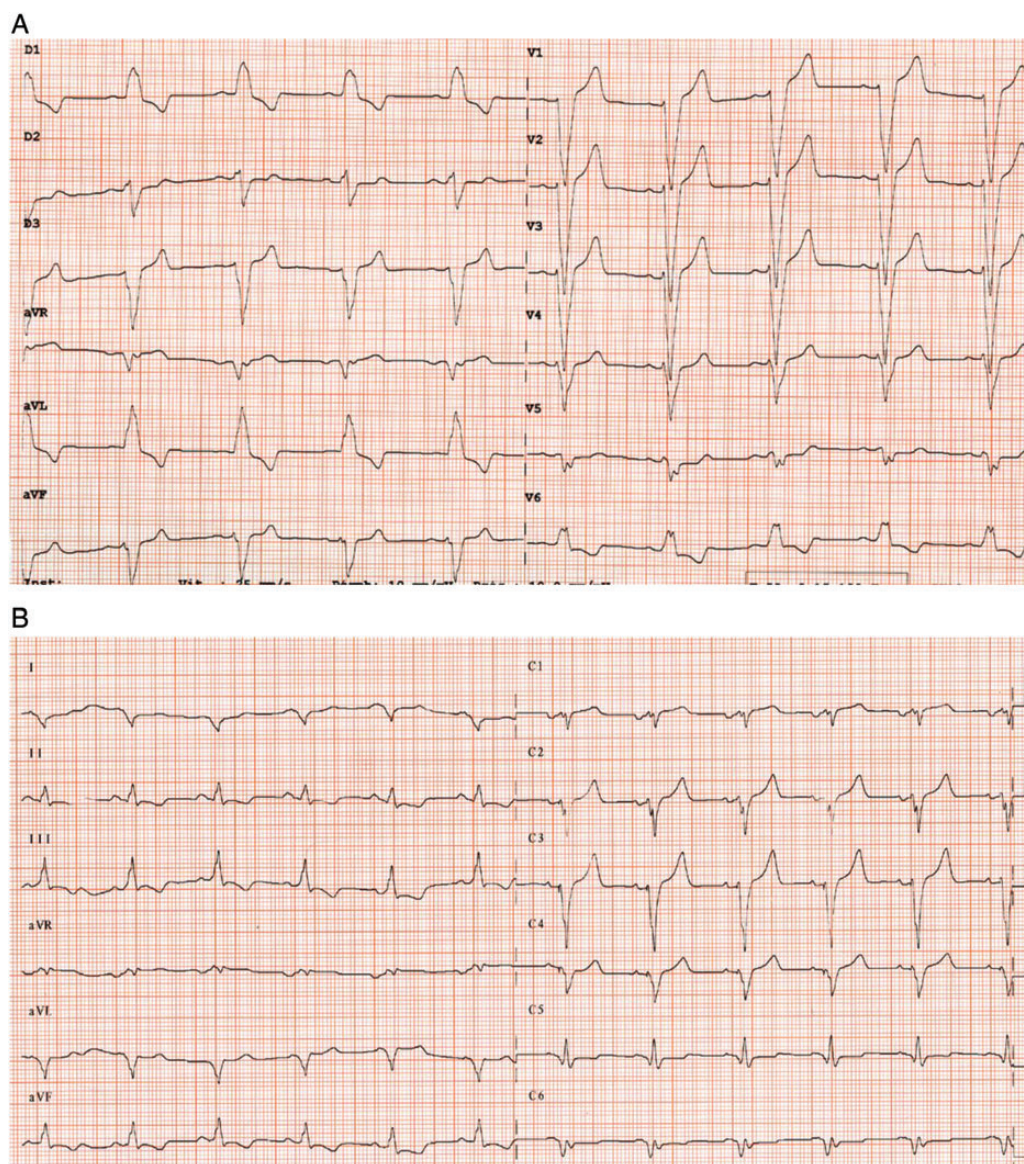


Figure 4 Twelve-lead ECGs of a patient with a quadripolar pacing lead with different programming timings. (A) Intrinsic rhythm with LBBB. (B) Conventional CRT with stimulation from a single (distal pole) of the quadripolar catheter (D1-M2) of MPP from a quadripolar lead. (C) Top: Multisite pacing with two LV vectors separated by 5 ms. (D) Multisite pacing with 50 ms delay between the two LV vectors. Changes in pacing configuration are associated with a significant change in QRS morphology and duration with narrowing of QRS and loss of notching seen in chest leads.

of patients).⁶³ Electrical delay and changes in the QRS morphology of surface ECG (Figure 4) may also be useful for pacing configuration. Current devices can perform automatic measurements of RV–LV delays for each electrode, both during RV sensing as well as RV pacing, which takes ~60–90 s. It seems logical that the electrode with the greatest electrical delay should be included in the pacing configuration, but the choice of the second LV electrode is less obvious. Also, it is unclear whether it is best to measure the delays during RV sensing or pacing. Another unanswered question is whether sequential pacing (i.e. delay between the two LV electrodes, and LV–RV delay) is better than simultaneous pacing. Studies evaluating sequential biventricular pacing for conventional CRT have not demonstrated

superiority compared with simultaneous pacing.^{82–84} Sequential MSP may not offer any added benefit compared with simultaneous pacing, unless other factors such as latency are to be considered in individual patients. If the ideal pacing configuration can be determined based upon electrical delays, it would be useful to have an algorithm that automatically proposes the best settings to facilitate programming.

Another useful feature is automatic measurement of thresholds to guide programming to reduce battery consumption. Quadripolar CRT-D systems are currently able to automatically perform thresholds from a variety of configurations and to indicate their impact on device longevity (taking into account the impedance measurements).

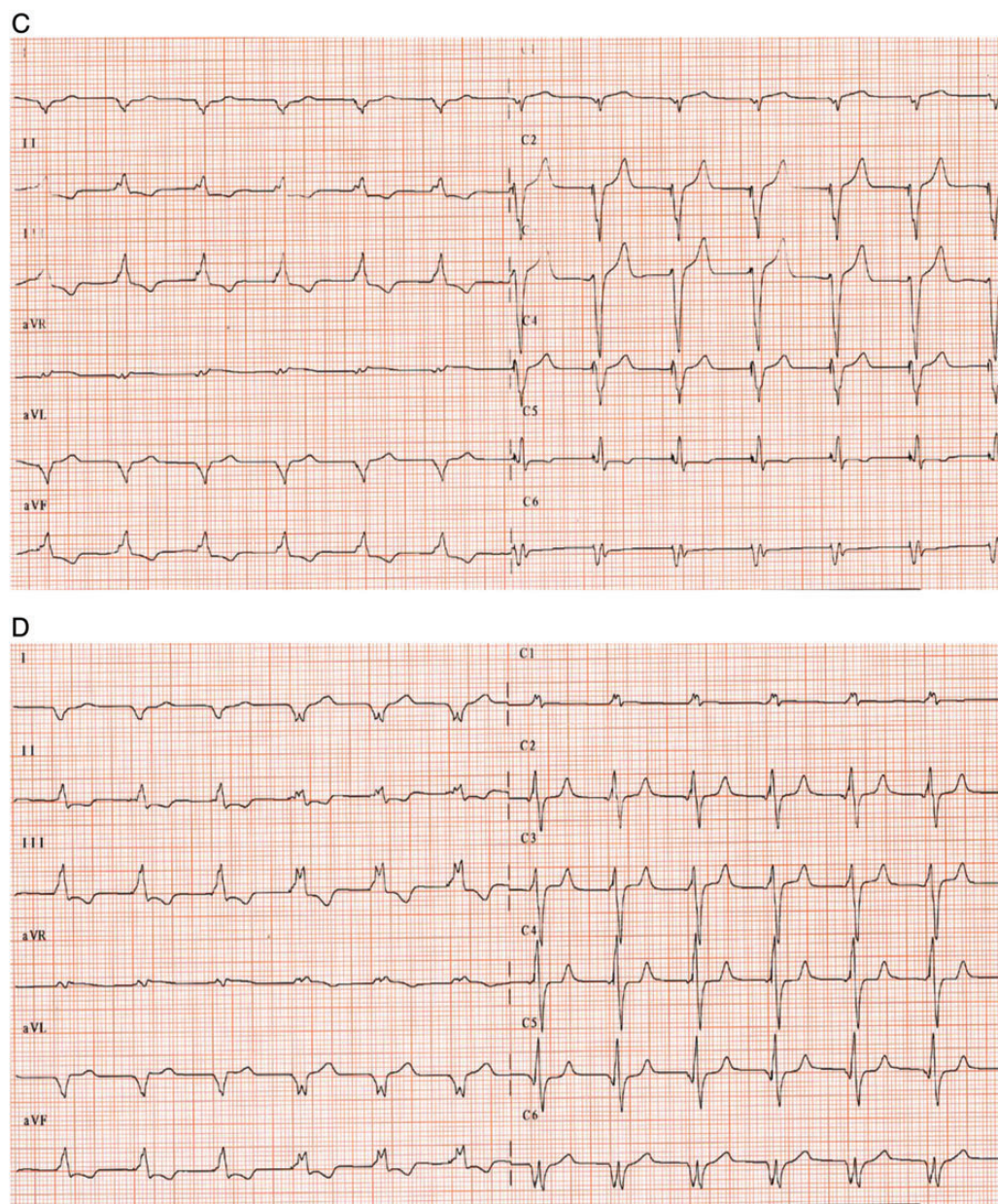


Figure 4 Continued

Summary

Non-response to CRT remains a significant problem and therefore there will be further efforts to reduce this. Multisite pacing would appear to be one way of potentially overcoming non-response in addition to other novel stimulation techniques such as LV endocardial pacing. The venous anatomy will always be a determinant of response, as it remains the gateway to the epicardium and thereby a determinant of how the LV lead lies across the ventricular wall. Whether pacing two electrodes along the posterolateral wall (apex and mid-ventricular region) has a greater haemodynamic impact as compared with pacing the distal electrode in the mid-ventricular segment of the anterolateral wall and basal segment of the

posterolateral wall is unclear. The interaction between the electroanatomical activation pattern, myocyte response, and several other covariates will all determine this response. It is quite likely that there will not be a one-size-fit all response and that individualizing the pacing strategy using outcome surrogates will be needed. Similarly, the relatively small proximal-to-distal electrode spacing of 'multipolar single-vein' stimulation may be inadequate in terms of the overall cardiac size and inter-patient differences.

Another important factor that may influence response to pacing is the myofibrillar pattern and recognizing the 'twisting motion' of the heart. Whether MSP should be confined to the epicardium alone is another important question for the future. One could speculate that a combination of endocardial and epicardial pacing may enable

better and more physiological recruitment of the myocardium, and could be a potential strategy in non-responders. Multipolar leads are likely to be the way forward compared with multiple leads as they offer a less complicated and technically more straightforward way of delivering MSP. At present, multipolar leads have been shown to be easily implantable and can avoid PNS and it is fair to say that they have already become the standard of care in delivering CRT. It should be highlighted that 'multi-polar' leads have been specifically designed and developed, in the past years, while 'multi-vein' must be considered experimental at its current state, with no dedicated industry developments in this field, neither for specific delivery needs nor fixation in the tributaries. Whether true MSP delivered by such leads will offer incremental benefit has been suggested albeit in small studies with limited follow-up. Many of the studies stated use acute haemodynamic data; the link, however, between acute haemodynamic measures and long-term outcome is not yet proven.^{27,85} Whether MSP will translate into longer-term clinical benefits is a yet unknown and will require the results of large ongoing studies to see if such treatment may offer benefit above and beyond conventional CRT.

Acknowledgements

This review was prepared by a writing group which was invited on behalf of the European Heart Rhythm Association Education Committee. This document was supported by a grant from St Jude Medical; however, the content has not been influenced in any way by its sponsor.

Conflict of interest: B.T. is a member of the speakers bureau for St Jude Medical and Medtronic. A.R. is currently involved in research sponsored by Medtronic and Boston Scientific. A.R. employs a Device Fellow sponsored by Medtronic. A.R. is also a member of the speakers' bureau for Medtronic. H.B. receives speaker's fees and research grants from Biotronik, Boston Scientific, Medtronic, Sorin, and St Jude Medical. C.A.R. receives research funding and Honoraria from St Jude Medical, Medtronic, and Boston Scientific. A.C. receives research funding and is consultant to Boston Scientific, Biotronik, Medtronic, St Jude Medical, and Sorin Group. D.G. receives consultancy fees and research support from Medtronic, St Jude Medical, Boston Scientific, and Biotronik. J.S. receives research funding and is consultant to Boston Scientific, Biotronik, Medtronic, St Jude Medical and Sorin Group. J.P.S. receives research funding and is consultant to Boston Scientific, Biotronik, Medtronic, St Jude Medical, and Sorin Group. M.B. receives research funding and is consultant to Boston Scientific, Biotronik, Medtronic, St Jude Medical, and Sorin Group. P.B. is a consultant for Medtronic. C.L. receives speakers fees and research grants from St Jude Medical; Medtronic; Biotronik; Sorin and Boston-Scientific.

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EP CASE EXPRESS

doi:10.1093/europace/euu270

Online publish-ahead-of-print 27 October 2014

The role of surface electrocardiogram after complex left atrial arrhythmias' ablation: behind electrical mechanisms

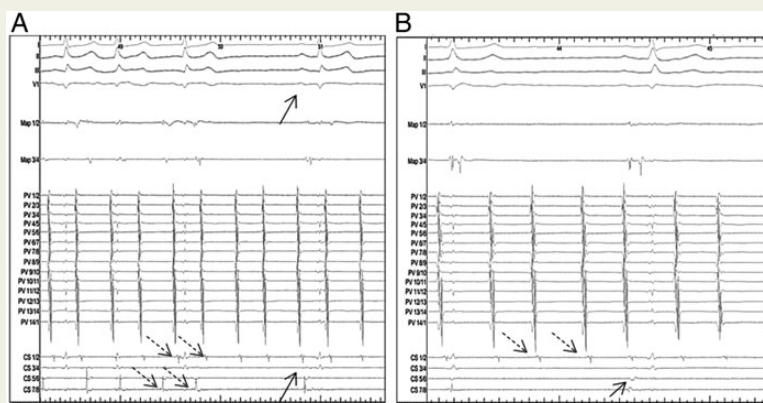
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We report of an interatrial dissociation after two relatively limited left atrial ablations for paroxysmal atrial fibrillation (PAF), with sinus rhythm in the right atrium (RA) and ongoing atrial tachycardia in the left atrium (LA). Patients suffering from PAF are supposed to have less electrical and anatomical remodelling, however the role of low-voltage and scar areas with functional conduction block in these patients is still ongoing discussion.

We report of an interatrial dissociation after two relatively limited LA endocardial ablation procedures, performed in a 64-year-old woman for PAF since 1 year. The patient underwent a successful pulmonary vein isolation (PVI), and 3 months later she developed symptomatic persistent AF requiring a second ablation. The patient underwent a re-PVI and limited ablation of complex fractionated atrial electrograms in LA, including the coronary sinus (CS) region, but none septally. During ablation, AF converted into an organized AT, resulting in two consecutive left localized re-entries, both related to a slow conduction zone within spontaneous low voltage area. After ablation at the anterior wall, surface ECG showed a conversion into sinus rhythm, whereas intracardiac electrograms revealed complete electric inter-atrial (left to right atrium) dissociation (Figure, panel A). Sinus rhythm in the RA was recorded at the proximal CS catheter (CS ostium), while ongoing AT was recorded from the circular mapping catheter (left atrial appendage) and from the distal CS catheter (inferior perimitral LA) (Figure, panel B). We performed an electrical cardioversion with restoration of sinus rhythm in both atria. During a 5-month follow-up the patient had no arrhythmia recurrences on Holter ECG monitoring. However, one might question the role of surface ECG regularly performed during her long term follow-up, since a recurrence of (only) left atrial arrhythmia would have been unrecognizable.



The full-length version of this report can be viewed at: http://www.escardio.org/communities/EHRA/publications/ep-case-reports/Documents/the_role_of_surface.pdf.